Session D2: Molecular Targeted Therapy: Biomarkers

Thursday, September 6

D2-01 Molecular Targeted Therapy: Biomarkers, Thu, 12:30 - 14:15

Prospective trial of preoperative gefitinib to correlate response with EGFR exon 19 and 21 mutations and to select patients for adjuvant gefitinib

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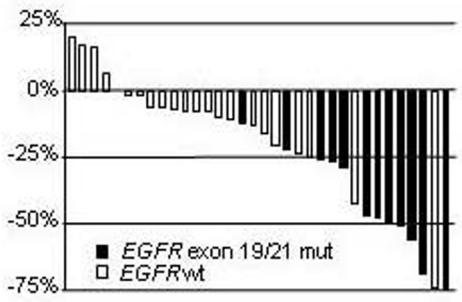
Background: Induction therapy provides a unique opportunity to evaluate therapies in patients with NSCLC to personalize care and facilitate drug research. We designed this 50 patient prospective trial to correlate response with gefitinib measured by CT with mutations in EGFR exons 19 and 21 and to simultaneously assess the agent's ability to induce regressions preoperatively in persons with NSCLC. To do this, we enriched the group studied to select individuals with tumors more likely to harbor EGFR mutations.

Methods: Patients with stage I or II NSCLC have a baseline chest CT and a core-needle biopsy to detect EGFR mutations. All participants smoked cigarettes 10 pack years and/or had tumors with bronchioloalveolar features. All receive gefitinib 250 mg daily. After 21 days, the CT is repeated and resection follows. Surgical specimens are again assayed for EGFR mutations and KRAS mutations. Patients with mutation and/or 25% regression (WHO) are given gefitinib for 2 years.

Results: Among 34 patients enrolled to date, EGFR mutations were detected in 12(35%); results were identical in 17/17 matched core biopsy and resection specimens. Thirteen (38%) had a 25% bidimensional tumor reduction after 21 days. The mutation rate was 77% in responding patients and 10% in patients without response, P=0.0001 for the primary study endpoint. The regression observed after 21 days of gefitinib and the correlation with EGFR mutation for each patient is shown in the figure. 0/3 patients with KRAS mutations had response or EGFR mutation. No increase in perioperative complications occurred. 15 patients received gefitinib postoperatively.

Conclusions: In this ongoing trial, 1) The rate of EGFR mutation was significantly higher in patients with response to gefitinib. 2) Our enrichment strategy resulted in the detection of three times the expected number of EGFR mutations in USA patients with NSCLC. 3) Gefitinib sensitivity can be assessed by CT in 21 days. 4) Results of mutation detection were identical in pre- and post-treatment specimens. Support: CA05826, CA113653.



D2-02 Molecular Targeted Therapy: Biomarkers, Thu, 12:30 - 14:15

Excision repair cross complementing 6 (ERCC6) single nucleotide polymorphism (SNP) and outcome to gemcitabine(gem)/ cisplatin(cis) or docetaxel(doc)/cis in stage IV non-small-cell lung cancer (NSCLC) patients (p)

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Background: ERCC6 (alternate name CSB) is involved in both transcription coupled and base excision DNA repair, and the ERCC6 C-6530>G SNP is involved in gene regulation. Different levels of ERCC6 mRNA expression have been observed in cells according to ERCC6 - 6530 genotype.

Methods: We investigated the ERCC6 C-6530>G SNP in 309 stage IV NSCLC p treated with doc/cis (196 p) and gem/cis (113 p). DNA was extracted from peripheral lymphocytes and Taqman assay was used for SNP typing.

Results: Distribution of ERCC6 genotypes was: CC 113 p (36.6%); CG 157 p (50.8%); GG 39 p (12.6%). No differences in genotype were observed according to age, gender, performance status (PS), histology, chemotherapy regimen or second-line treatment. Overall time to progression (TTP) was 5.4 months (m) and median survival (MS) 9.9 m. No differences in TTP or MS were observed according to ERCC6 SNP types. However, when p were broken down by chemotherapy regimen, TTP was 7 m for 31 CC p treated with gem/cis and 5.4 m for 71 CC p treated with doc/cis (P=0.04) (Table). MS was longer for CC p treated with gem/cis (11 m) than for CC p treated with doc/cis (8.9 m) (P=0.46). Differences were also observed in p with PS 0 and in younger p.

Conclusions: ERCC6 C-6530>G SNP may confer differential sensitivity to gem or doc in combination with cis. We hypothesize that ERCC6 6350 CC is a surrogate of ERCC6 transcript, where lower ERCC6 expression levels may increase the activity of gem/cis in comparison to doc/cis.

ERCC6	N	TTP	95% CI	P
CC				0.04
Doc/Cis	75	5.4 m	3.1 - 7.7	
Gem/cis	31	7 m	2.5 - 11.4	
GG				0.90
Doc/cis	22	5.9 m	4.3 - 7.5	
Gem/cis	17	4 m	0.4 - 7.6	
CG				0.95
Doc/cis	99	5.2 m	4 - 6.4	
Gem/cis	56	6 m	4.8 - 7.2	